

Effect of beta-adrenergic blockade with carvedilol on cachexia in severe chronic heart failure: results from the COPERNICUS trial

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Abstract

Background Cardiac cachexia frequently accompanies the progression of heart failure despite the use of effective therapies for left ventricular dysfunction. Activation of the sympathetic nervous system has been implicated in the pathogenesis of weight loss, but the effects of sympathetic antagonism on cachexia are not well defined.

Methods We prospectively evaluated changes in body weight in 2289 patients with heart failure who had dyspnoea at rest or on minimal exertion and a left ventricular ejection fraction <25%. Patients were randomly assigned (double-blind) to receive either placebo ($n = 1133$) or carvedilol ($n = 1156$) and were followed for the occurrence of major clinical events for up to 29 months (COPERNICUS trial). Patients were not enrolled if they had signs of clinically significant fluid retention due to heart failure.

Results Patients in the carvedilol group were 33% less likely than patients in the placebo group to experience a further significant loss of weight ($>6\%$) (95% confidence interval: 14–48%, $P = 0.002$) and were 37% more likely to experience a significant gain in weight ($\geq 5\%$) (95% confidence interval: 12–66%, $P = 0.002$). Carvedilol's ability to prevent weight loss was most marked in patients with increased body mass index at baseline, whereas its ability to promote weight gain was most marked in patients with decreased body mass index at baseline. Increases in weight were not accompanied by evidence of fluid retention. Baseline values for body mass index and change in body weight were significant predictors of survival regardless of treatment.

Conclusions Carvedilol attenuated the development and promoted a partial reversal of cachexia in patients with severe chronic heart failure, supporting a role for prolonged sympathetic activation in the genesis of weight loss.

Keywords Cardiac cachexia; Heart failure; Carvedilol; Sympathetic nervous system; COPERNICUS trial; Weight loss

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Introduction

Loss of weight is common in patients with untreated chronic heart failure and appears to happen early in the course of the disease. The weight loss affects all body compartments, and is important because muscle bulk is strongly related to

exercise capacity, and hence a patient's symptoms,¹ and because both decreasing weight and weight loss are strongly related to an adverse prognosis.²

Cachexia is used to describe involuntary weight loss secondary to disease states. Any definition requires an arbitrary cut-off, and a commonly used definition is weight loss of at

least 5% in 12 months.³ Cachexia accompanies a number of disease states, including heart failure, and is associated with a particularly poor prognosis. Although the causes of weight loss and ultimately cachexia are not clear, the sympathetic nervous system is activated in cachectic patients and has been implicated in the development of muscle wasting.⁴⁻⁶ Uncontrolled reports have suggested that β -adrenergic blockade can attenuate muscle catabolism and lead to weight gain in selected patients with cardiac and non-cardiac disorders,⁷ and other work has suggested that other agents that interfere with neurohormonal activation in heart failure, such as angiotensin converting enzyme inhibitors, are also associated with a lower risk of weight loss.⁸

We wanted to explore the effects of sympathetic blockade on cardiac cachexia in a prospectively designed sub-study of a large-scale clinical trial of the α_1 -/ β_1 -/ β_2 -receptor antagonist, carvedilol, in patients with severe chronic heart failure.

Methods

Study design

We prospectively evaluated the patients enrolled in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, the design and primary results of which have been previously published.⁹ A total of 2289 patients with dyspnoea at rest or on minimal exertion and a left ventricular ejection fraction <25% despite appropriate therapy were randomly assigned (in a double-blind fashion) to receive either

placebo ($n = 1133$) or carvedilol ($n = 1156$) and were followed for the occurrence of major clinical events for up to 29 months. Patients were not enrolled if they had signs of clinically significant fluid retention (rales, ascites, or more than minimal peripheral oedema) at the time of randomization, unless the fluid retention was deemed due to of a non-cardiac cause.

Following randomization, patients received an initial dose of 3.125 mg of placebo or carvedilol twice daily for 2 weeks, which was then increased at 2-week intervals (if tolerated), first to 6.25 mg, then to 12.5 mg, and finally to a target dose of 25 mg twice daily. Each patient then entered a maintenance phase, during which they were seen every 2 months until the end of the study. Height and weight were measured at baseline, and weight was measured every 2 weeks during up-titration and every 2 months during the maintenance phase. Throughout the trial, investigators were encouraged to adjust the dose of concomitant diuretic continually to maintain euolemia and dry weight.

Statistical analysis

The primary endpoint of COPERNICUS was all-cause mortality. A detailed analysis of the prognostic importance of and the effect of treatment on weight loss was prospectively defined prior to completion of the trial.

Patients in the trial were grouped according to their baseline body mass index (defined as weight [in kilogrammes] divided by the square of the height [in metres]) into the following pre-specified categories: <22 kg/m² (underweight), 22 to <25 kg/m² (ideal weight), 25 to <30 kg/m² (overweight), and ≥ 30 kg/m² (obese). Five patients with missing

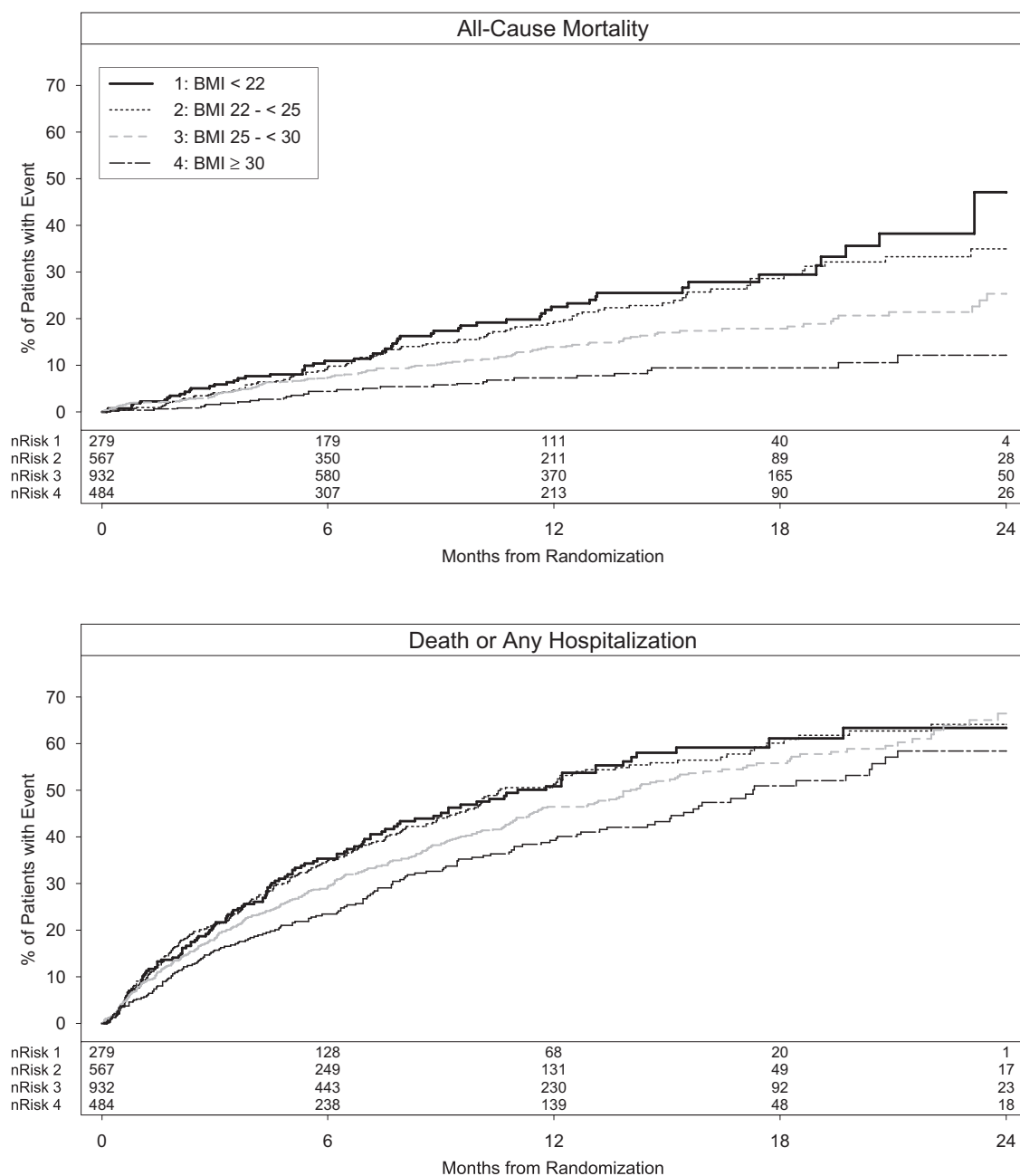
Table 1 Baseline characteristics of patients in body mass index subgroups

	Baseline body mass index (kg/m ²)			
	<22	22 to <25	25 to <30	≥ 30
Number of patients	279 (12.3%)	567 (25.1%)	932 (41.2%)	484 (21.4%)
Age (years)*	67.4 \pm 12.1	64.5 \pm 11.6	63.1 \pm 10.8	59.7 \pm 11.1
Gender (% men)*	70.3	82.2	82.0	78.1
Duration of heart failure (years)	2.5 \pm 2.7	2.7 \pm 3.4	2.7 \pm 3.2	2.6 \pm 2.7
Ischaemic aetiology (%)*	61.3	71.4	69.6	60.3
LV ejection fraction (%)	19.1 \pm 4.4	19.8 \pm 3.8	20.0 \pm 3.6	20.0 \pm 4.5
Heart rate (beats/min)*	83.1 \pm 12.7	82.1 \pm 12.7	81.9 \pm 11.7	85.5 \pm 12.9
Systolic BP (mmHg)*	115.2 \pm 18.1	120.3 \pm 17.9	125.3 \pm 18.3	127.9 \pm 19.1
Diastolic BP (mm Hg)*	72.1 \pm 10.1	74.8 \pm 10.6	77.1 \pm 10.4	79.6 \pm 11.4
Serum sodium (mmol/L)	137.0 \pm 2.8	136.7 \pm 2.8	136.8 \pm 2.6	137.0 \pm 2.8
Serum creatinine (μ mol/L)*	136.8 \pm 43.4	134.9 \pm 38.3	134.3 \pm 33.3	128.6 \pm 34.5
Haemoglobin (g/dL)*	13.3 \pm 1.7	13.8 \pm 1.8	14.0 \pm 1.6	14.1 \pm 1.8
Concomitant medications (%):				
Digitalis*	76.3	67.5	61.9	65.5
Diuretics	98.9	98.4	99.5	99.2
ACEI/ATII*	94.3	97.4	97.3	98.8
Spironolactone	20.1	20.6	18.0	20.7
Amiodarone	17.2	19.6	16.5	16.9

ACEI/ATII = angiotensin converting enzyme inhibitor or angiotensin II antagonist; BP = blood pressure; LV = left ventricular. Continuous data are expressed as means \pm standard deviations.

*Differences are statistically significant among subgroups ($P < 0.05$).

Figure 1 Kaplan–Meier cumulative incidence curves for all-cause mortality in subgroups defined by pre-treatment body mass index (BMI) (placebo and carvedilol groups combined).



baseline values for height or weight and 22 patients with oedema at baseline were excluded from all analyses as were any weights recorded during follow-up if oedema were present (4.8% of 18 448 weight measurements). Baseline characteristics among the four subgroups for body mass index were compared using the Kruskal–Wallis test for continuous variables and the chi-squared test for categorical variables.

The effect of treatment on change in body weight was evaluated at each visit using the Wilcoxon rank sum test. We defined loss of body weight from baseline of >6% as being important weight loss: we chose to use a higher cut-off than the more usual 5% to be certain we were only including significant change in weight given that weight may fluctuate in patients with chronic heart failure because of

changes in fluid status. Gain in body weight of $\geq 5\%$ from baseline was defined as clinically significant. The time to these weight-change events was estimated using linear interpolation between weight measurements, and follow-up time for patients with no event was censored on the date of the last recorded weight measurement.

Cumulative incidence curves for all-cause mortality and weight change events were constructed by the Kaplan–Meier method. The relationships between pre-treatment body mass index, the effect of treatment with carvedilol, and the risk of clinical events were examined using Cox proportional hazards regression models with pre-treatment body mass index included as a continuous variable. A treatment group by pre-treatment body mass index interaction term was included in the models to assess the influence of pre-treatment body mass index on the magnitude of the treatment effect. These models were also used to estimate hazard ratios and 95% confidence intervals. The relationship between weight change during the study and all-cause mortality was examined by including a time-dependent covariate for weight change from baseline in the Cox model, using interpolated weight values at each failure time.

It should be noted that analyses of weight gain and weight loss during the study ignore the competing risk of death and the effect that differences in survival have on the type of patient at risk across time. Considering the survival benefit of carvedilol, however,⁹ these analyses are biased in favour of placebo and therefore underestimate any effect of carvedilol.

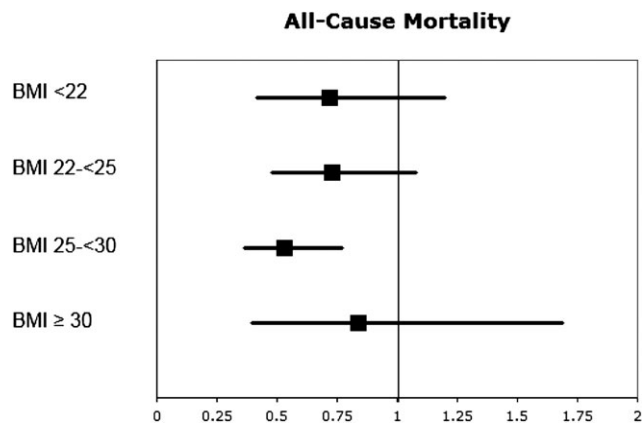
All reported *P* values are two-sided and nominal.

Results

The baseline characteristics of subgroups defined by baseline body mass index are shown in Table 1. At the beginning of the study, 279 patients (12.3%) were underweight (body mass index <22), and 484 patients (21.4%) were obese (body mass index ≥ 30). Patients who were underweight were most likely to have the most advanced heart failure as reflected by their greater age, higher heart rate and serum creatinine, lower blood pressure and haemoglobin, and more frequent use of digitalis and less frequent use of drugs interfering with the renin–angiotensin system.

The lower the body mass index, the higher the risk of death, regardless of treatment (Figure 1). For each unit increase in body mass index, the risk of death decreased by 7.7% ($P < 0.0001$). Carvedilol reduced the risk of death by 35% (from 19.7 to 12.8 per cent per patient-year of follow-up, $P < 0.001$), and the magnitude of this benefit did not vary as a function of pre-treatment body mass index (interaction *P* value = 0.97, Figure 2).

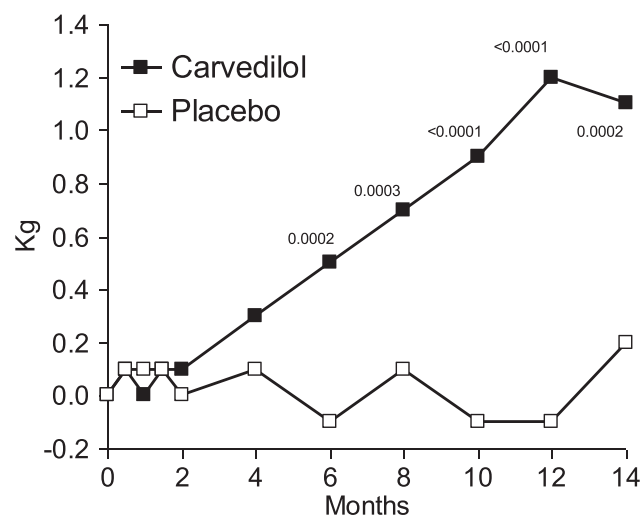
Figure 2 Hazard ratios and 95% confidence intervals for the effect of carvedilol on all-cause mortality in subgroups defined by pre-treatment body mass index (BMI). Hazard ratios <1.0 indicate lower risk in the carvedilol group.



Effect of carvedilol on changes in body weight

During the course of follow-up, patients in the carvedilol group gained weight when compared with patients in the placebo group. The difference between the two groups became statistically significant approximately 6 months following randomization and increased in magnitude with increased duration of follow-up (Figure 3). After approximately 1 year of treatment, weight increased in carvedilol-treated patients by 1.2 ± 0.2 kg, as compared with a slight loss of weight of 0.1 ± 0.2 kg in placebo-treated patients, $P < 0.0001$.

Figure 3 Mean change in body weight from baseline at specified times during follow-up in the carvedilol (filled squares) or placebo (open squares) groups. The *P* values denote significance for the comparison between groups.



Patients in the carvedilol group were less likely than patients in the placebo group to experience a loss of weight >6% during the course of follow-up (Table 2 and Figure 4). A critical loss of weight occurred in 145 patients in the placebo group but only 110 patients in the carvedilol group—a 33% lower risk of clinically significant weight loss due to treatment with carvedilol (95% confidence interval, 14–48% lower risk, $P = 0.002$, Figure 3). The effect of carvedilol was most marked in patients with an increased baseline body mass index (Table 2).

Patients in the carvedilol group were more likely than patients in the placebo group to experience a gain in weight of $\geq 5\%$ (Table 2 and Figure 4). A critical gain in weight occurred in 234 patients in the carvedilol group but in only 167 patients in the placebo group—a 37% greater likelihood risk of clinically significant weight gain as a result of treatment with carvedilol (95% confidence interval, 12–66% lower risk, $P = 0.002$, Figure 3). The effect of carvedilol was most marked in patients with a decreased body mass index at baseline (Table 2).

Prognostic importance of weight changes

Although change in body weight during the study predicted survival independent of treatment assignment (carvedilol vs. placebo) or pre-treatment body mass index (data not shown), comparison of the hazard ratios for treatment assignment in the model that included the time-dependent covariate for weight change (hazard ratio = 0.69) or did not include weight change (hazard ratio = 0.65) suggested that only a small portion of the benefit of carvedilol on survival was attributable to its effect on body weight.

Discussion

We have found strong evidence that one class of drugs with established efficacy in the treatment for heart failure (specifically, beta-adrenergic blocking drugs) can ameliorate the

syndrome of cardiac cachexia. In a large-scale controlled clinical trial, long-term treatment with carvedilol not only markedly reduced the risk of further weight loss but also led to meaningful reversal of cachexia in many patients with advanced left ventricular dysfunction.

The beneficial effects of beta-adrenergic blockade on the syndrome of cardiac cachexia are consistent with earlier reports that postulated an important role for the sympathetic nervous system in the development of cardiac cachexia (The role of the sympathetic nervous system was reviewed in¹⁰). Activation of the sympathetic nervous system is associated with the development of cachexia in patients with cancer.^{11,12} Patients with heart failure have marked sympathetic nervous system activation, and plasma norepinephrine is even higher in heart failure patients with cachexia as compared with heart failure patients without muscle wasting.⁷

Increased sympathetic activity can contribute to cachexia by increasing total body energy expenditure,¹³ which can be reduced with β -blockade,¹⁴ and by exerting direct myotoxic effects on skeletal muscle,^{15,16} again attenuated by beta-blockade.¹⁸ Blockade of β_2 -receptors seems to have a more profound effect than blockade of β_1 -receptors.^{5,18} In addition, sympathetic activation can decrease the secretion of leptin,¹⁷ exacerbate insulin resistance,¹⁸ and promote the release of proinflammatory cytokines,¹⁹ all of which can lead to wasting of adipose and muscle cells.

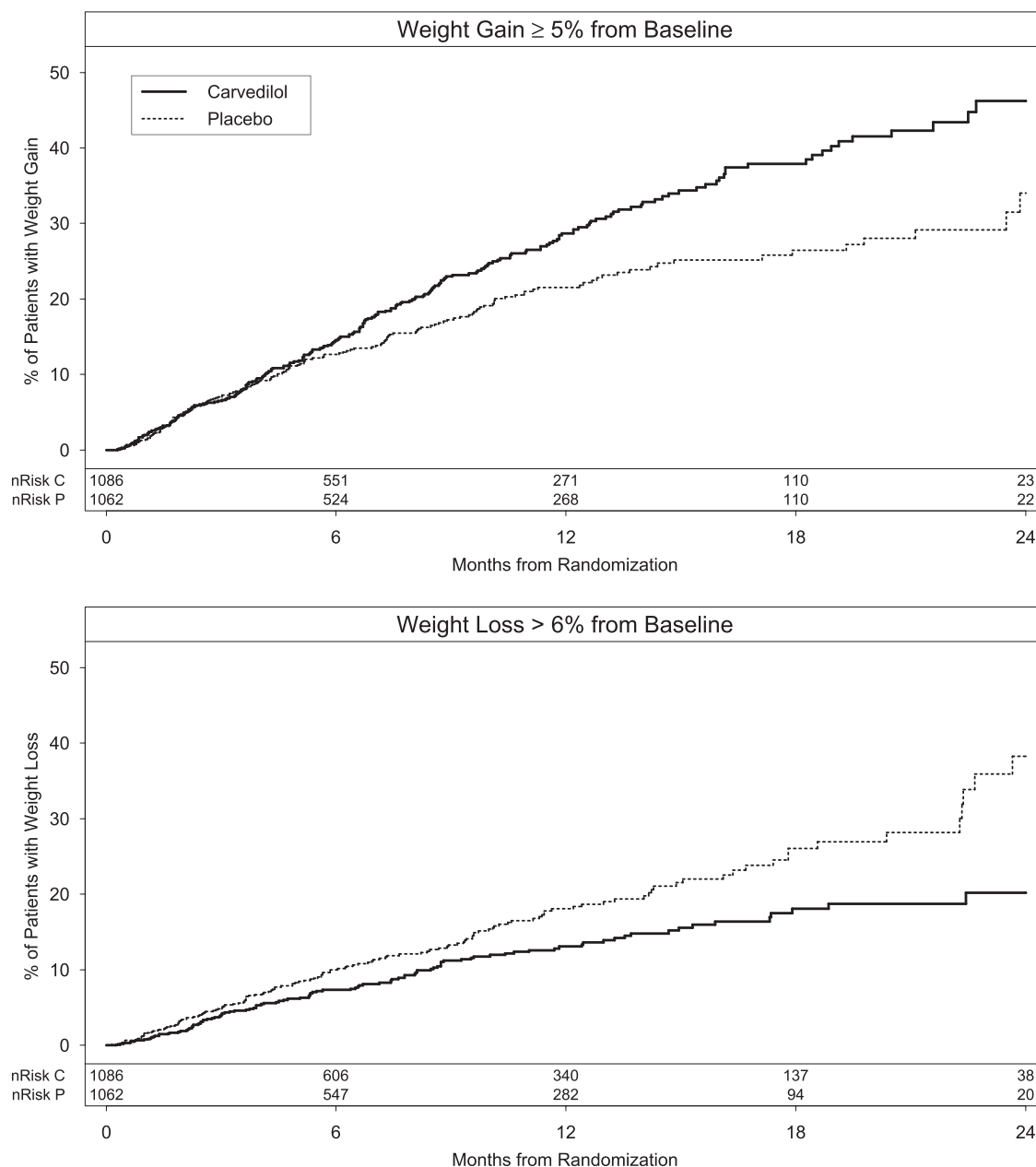
Beta-blockade is thus a logical approach to managing the problem of weight loss and cachexia. Carvedilol's ability to prevent weight loss was most marked in patients who were overweight at baseline, whereas its ability to promote weight gain was most marked in patients who were underweight at baseline. This difference between treatment groups was apparent, even though patients were more likely to die on placebo, which would have been expected to minimize the retention of high-risk cachectic patients in the placebo group. The effects of carvedilol on cachexia were greater than those previously reported with an angiotensin converting-enzyme inhibitor⁸ but were seen in patients already receiving such treatment. These data therefore represent the first clinical

Table 2 Frequency of weight gain and weight loss during follow-up in the placebo and carvedilol groups

	Baseline body mass index (kg/m ²)			
	<22	22 to <25	25 to <30	≥ 30
Weight gain $\geq 5\%$				
Placebo	30/125 (31%)	50/278 (24%)	58/430 (21%)	29/229 (15%)
Carvedilol	60/136 (59%)	63/265 (30%)	74/453 (21%)	37/232 (25%)
Carvedilol:placebo hazard ratio (95% CI)	2.20 (1.41–3.43)	1.23 (0.85–1.79)	1.11 (0.79–1.57)	1.48 (0.91–2.41)
Weight loss >6%				
Placebo	16/125 (19%)	34/278 (19%)	57/430 (17%)	38/229 (19%)
Carvedilol	16/136 (17%)	32/265 (17%)	41/453 (11%)	21/232 (11%)
Carvedilol:placebo hazard ratio (95% CI)	0.90 (0.44–1.81)	0.86 (0.53–1.40)	0.59 (0.39–0.88)	0.56 (0.33–0.96)

CI = confidence interval. These analyses are restricted to patients with at least one weight measurement during follow-up ($n = 2148$) and do not account for the risk of death as a competing factor. Percentages are 1-year Kaplan–Meier event rates.

Figure 4 Kaplan–Meier cumulative incidence curves for the occurrence of at least a 5% weight gain and for greater than 6% weight loss in the placebo and carvedilol groups. Patients treated with carvedilol were 37% more likely to experience significant weight gain ($P = 0.002$) and 33% less likely to experience significant weight loss ($P = 0.001$).



trial demonstrating that the development of cardiac cachexia can be both slowed and ameliorated in patients with chronic heart failure.

Our results are similar to those seen more recently in a trial of beta-blockade in patients with cachexia due to cancer. In ACT ONE, the beta-blocker espendolol was given to 87 patients with cancer-related cachexia for 16 weeks in a randomized, double blind, trial.^{20,21} Patients who received

higher dose espendolol gained weight whilst patients on placebo continued to lose weight. There was a significant increase in lean body mass, rather than fat mass, and there was a suggestion that higher dose espendolol was associated with a better prognosis.

There is an extensive literature on the 'obesity paradox' of heart failure—that is, the apparently paradoxical relation between increasing weight and better survival. The relation

between increasing weight and improved prognosis has been shown both in patients with chronic²² and those with acute heart failure.²³ It may be that the apparent paradox is (at least in part) an artefact: studies have been retrospective; patients who are obese may become breathless earlier (and hence present earlier) than those with normal weight; and obese patients by virtue of higher blood pressure might be better able to tolerate higher doses of disease-modifying medication. However, weight loss is also associated with a poor prognosis, particularly in those patients who are obese at baseline.²⁴

Limitations

Our findings should be interpreted cautiously for two reasons. First, as has been performed in earlier reports, cachexia was defined as changes in body weight, but changes in weight can be related to shifts in fluid, particularly in patients with heart failure. This possibility led us to exclude from our analyses any data collected at times when patients experienced clinically important fluid retention. Such exclusion occurred infrequently, however, because patients with pre-existing fluid retention were excluded (by protocol design) at the start of the study and because investigators were strongly encouraged to adjust the dose of concomitant diuretic continually to maintain dry weight throughout the trial.

Second, the effects of carvedilol on body weight may not have reflected a specific adrenergic effect on the metabolism

of adipose tissue or skeletal muscle but may have been related to an increase in physical activity^{25,26} or improvement in nutrition²⁷ that might accompany a reduction in symptoms in heart failure. However, exercise tolerance has not been consistently improved with carvedilol in clinical trials in heart failure,^{28–30} and treatments that have improved symptoms and exercise tolerance have not produced striking effects on cachexia.

Acknowledgements

The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015.³¹

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Conflict of Interest

A.L. Clark, A.J.S. Coats, H. Krum, H.A. Katus, P. Mohacsi, D. Salekin, M.K. Schultz, M. Packer, and S.D. Anker declared that they had no conflict of interest.

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